a podophyllotoxin selected from the group consisting of etoposide and teniposide; and tocoferol covalently linked to a water-soluble polymer; with the proviso that free tocoferol is not present.

REMARKS

Claims 1, 4, and 7-24 are pending. The Applicants herein respectfully request further examination of the application and reconsideration of the rejection of the claims, in view of the amendments and following remarks.

The Examiner has alleged that the subject matter of these claims is obvious under 35 USC§103(a) in view of the disclosure of Lambert, *et al.*, United States Patent No. 6,458,373 ('373).

The applicants respectfully emphasize to the Examiner that the disclosure of Lambert, *et al.*,'373, however, is limited to compositions that necessarily comprise *free* tocopherol. Particularly, in sharp contrast to the Applicants' invention, the disclosure of **Lambert, *et al.*,'373 is limited to compositions that *necessarily comprise* free tocopherol**, i.e., tocopherol AND a therapeutic agent -OR- tocopherol AND a surfactant AND a therapeutic agent.[2] In other words, *free* tocopherol is required in all embodiments taught by Lambert, *et al.*[3] The '373 disclosure, as

[2] Although paclitaxel is preferred, therapeutic agents contemplated by Lambert, *et al.*, include several extensive laundry lists of compounds, which include but are not limited to, Taxol (paclitaxel) and related molecules collectively termed taxoids, taxines or taxanes, Taxotere, Amonafide, Illudin S, 6-hydroxymethylacylfulvene Bryostatin 1, 26-succinylbryostatin 1, Palmitoyl Rhizoxin, DUP 941, Mitomycin B, Mitomycin C, Penclomedine. Interferon .alpha.2b, angiogenesis inhibitor compounds, Cisplatin hydrophobic complexes such as 2-hydrazino-4,5-dihydro-1H-imidazole with platinum chloride and 5-hydrazino-3,4-dihydro-2H-pyrrole with platinum chloride, vitamin A, vitamin E and its derivatives, particularly tocopherol succinate, 1,3-bis(2-chloroethyl)-1-nitrosurea ("carmustine" or "BCNU"), 5-fluorouracil, doxorubicin ("adriamycin"), epirubicin, aclarubicin, Bisantrene (bis(2-imidazolen-2-ylhydrazone)-9,10-anthracenedicarboxaldehyde, mitoxantrone, methotrexate, edatrexate, muramyl tripeptide, muramyl dipeptide, lipopolysaccharides, 9-b-d-arabinofuranosyladenine ("vidarabine") and its 2-fluoro derivative, resveratrol, retinoic acid and retinol, Carotenoids, tamoxifen, Palmitoyl Rhizoxin, DUP 941, Mitomycin B, Mitomycin C, Penclomedine, Interferon .alpha.2b, Decarbazine, Lonidamine, Piroxantrone, Anthrapyrazoles, Etoposide, Camptothecin, 9-aminocamptothecin, 9-nitrocamptothecin, camptothecin-11 ("Irinotecan"), Topotecan, Bleomycin, the Vinca alkaloids and their analogs [Vincristine, Vinorelbine, Vindesine, Vintripol, Vinxaltine, Ancitabine], 6-aminochrysene, and navelbine.

[3] Col.9, lines 13-16.

acknowledged by the Examiner, teaches *an emulsion of tocopherol*, stabilized by biocompatible surfactants. Formulations contemplated by Lambert, *et al.* in U.S. Patent No. 6,458,373 all require *free* tocopherol and are particularly developed, intended and preferred for the administration of Paclitaxel as a hydrophobic therapeutic. Formulations of the present invention, while being appropriate for podophyllotoxins, do not provide solubility to Paclitaxel, which is contrary to compositions described and contemplated by Lambert, *et al.*, in U.S. Patent No. 6,458,373. If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP §2143.01. The Examiner is referred to sections 14, 15 and 21 of the Rule 132 Declaration attached hereto.

It is respectfully pointed out that **the Applicants were the first to identify the ability to employ TPGS (d-α-tocopheryl polyetherylene glycol 1000 succinate), independently, to solubilize podophyllotoxins, *per se*, and to thereby form a stable dispersion having particularly valuable physical and therapeutic properties**. The Applicants' defined compositions and methods of treatment merely require a podophyllotoxin AND tocopherol *covalently linked* to a water-soluble polymer. See, e.g., Examples I-III, Specification pages 33-35. The prior art is devoid of tocopherol covalently linked to a water-soluble polymer to solubilize a podophyllotoxin such as etoposide for the production of the valuable and efficacious pharmaceutical composition or described methods of use thereof as described and exemplified by the Applicants. See, e.g., Examples XIII - XVI, Specification pages 38-43. **Furthermore, as demonstrated by the Applicants, and in contrast to the suggestion of Lambert, *et al.*, disclosure, ionic and non-ionic surfactants, POLOXAMERS for example, PLURONIC P85, PLURONIC 127, PLURONIC 123, PLURONIC 68, PLURONIC 108, 88, 61, polyethyleneimine-polyoxyethylene do not solubilize podophyllotoxin, and are in fact detrimental to the efficacy of podophyllotoxin pharmaceutical compositions**. See, e.g., Applicants' Examples IV-XII, Specification pages 35-38.

The '373 disclosure does not disclose or suggest effective formulations of podophyllotoxins, *per se*, as described by the Applicants.

Particularly, Lambert, *et al.*, Example 23 (Col.21), Etoposide Emulsion Formulation in Tocopherol is described as follows:[4]

Etoposide	4 mg
tocopherol	300 mg
TPGS	50 mg
Poloxamer 407	50 mg

As described in the Lambert, *et al.*, Summary of the Invention,[5] "the present invention is directed to pharmaceutical compositions including: tocopherol, a surfactant or mixtures of surfactants, with and without an aqueous phase, and a therapeutic agent wherein the composition is in the form of an emulsion, micellar solution or a self-emulsifying drug delivery system ... The pharmaceutical compositions can be stabilized by the addition of various amphiphilic molecules, including anionic, nonionic, cationic, and zwitterionic surfactants." Moreover, "surfactants" are defined by Lambert, *et al.*, specifically to designate "surface active group of amphiphilic molecules which are manufactured by chemical processes or purified from natural sources or processes. These can be anionic, cationic, nonionic, and zwitterionic." Col.4, line 66, *et seq.* These are further indicated to include Poloxamers or Pluronics, synthetic block copolymers of ethylene oxide and propylene oxide. Col.5, line 41, *et seq.*

Omission of an Element with Retention of Function Is an Indicia of Unobviousness. The claims now presented by the Applicants are specifically drawn toward compositions comprising a podophyllotoxin and tocoferol covalently linked to a water-soluble polymer, with the *proviso* that *free* tocopherol is not present. It is axiomatic that a claimed invention is not obvious solely because it is composed of elements that are all individually found in the prior art. Particular findings must be made as to the reason the skilled artisan, *with no knowledge of the claimed invention*, would have selected these components for combination in the manner

[4] Col.21, line 40, *et seq.*

[5] Col.3, line 46, *et seq.*

claimed.[6] See, e.g., In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998).

Free tocopherol and etoposide, *per se*, is unsatisfactory as a pharmaceutical composition. *Free* tocopherol (as would be required by Lambert, *et al.*,'373) is detrimental to properties and efficacy of podophyllotoxin compositions. The Applicants respectfully refer to the Rule 1.132 evidence presented herewith. The Examiner is respectfully referred to sections 7 and 8 of the Affidavit wherein Dr. Alakhov confirms and attests to the fact that the addition of alpha-tocopherol (*free* tocopherol) to formulations comprising Etoposide and TPGS dramatically reduces the solubility of Etoposide and lead to phase separation. See, section 16. Results are confirmed in sections 10-13 of the Declaration that aqueous pharmaceutical compositions comprising podophyllotoxin and TPGS wherein free tocopherol is not present, exhibits valuable anticancer properties and activity. Examples 14 and 15 (pages 40-42) of the written description further demonstrate unambiguously that the formulation of Etoposide and TPGS, wherein free tocopherol is not present, is more effective against lung carcinoma that VEPESID® (the clinically accepted formulation of Etoposide); *and*, more effective in reducing the number of metastases than the clinical VEPESID® formulation.

Accordingly, in summary, i) the formulations taught by Lambert '373 do not work physically or pharmacologically with the podophyllotoxins; and, ii) the formulations taught by the Applicants are physically and pharmacologically functional *and* exhibit significantly greater efficacy than the currently available accepted clinical standard.

In view of the amendments to the claims as well as the evidence and remarks presented herein, the Applicants respectfully request the Examiner to withdraw the rejection of the claims under Title 35 U.S.C. §103.

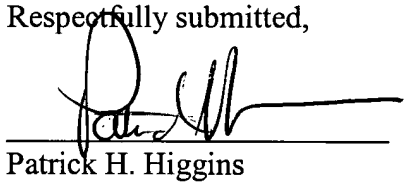
* * *

[6] Accordingly, it is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to "[use] that which the inventor taught against its teacher." W.L. Gore v. Garlock, Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

For the foregoing reasons, the Applicants submit that Claims 1, 4, and 7-24 are now in condition for allowance. Early action toward this end is courteously solicited. *The Examiner is kindly encouraged to telephone the undersigned in order to expedite any detail of the prosecution.*

A check in the amount of $465.00 to cover the cost of the three-month extension is enclosed. The Commissioner is authorized to charge any deficiency or credit any overpayment in connection herewith to Deposit Account No. 13-2165.

Respectfully submitted,



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Appendix

PENDING CLAIMS MARKED TO SHOW CHANGES

1. (Twice Amended) A fluid pharmaceutical composition comprising an aqueous dispersion of micelles having an average diameter less than about 300 nm, said micelles comprising: a podophyllotoxin selected from the group consisting of etoposide and teniposide, and [a surfactant selected from the group consisting of tocoferol and] tocoferol covalently linked to a water-soluble polymer; with the proviso that free tocoferol is not present.

4. (Amended) The fluid pharmaceutical composition of claim 1 wherein the podophyllotoxin is etoposide.

7. (Amended) The fluid pharmaceutical composition of claim 1 wherein the water-soluble polymer is poly-oxyethylene, poly-oxyethylene-poly-oxypropylene copolymers polyacrylamides, polyglycerols, polyvinylalcohols, polyvinylpyrrolidones, polyvinylpyridine N-oxides, copolymers of vinylpyridine N-oxide and vinylpyridine, polyoxazolines, polyacroylmorpholines or derivatives thereof.

8. (Amended) The fluid pharmaceutical composition of claim 1 wherein the water-soluble polymer is a polypeptide or derivative thereof.

9. (Amended) The fluid pharmaceutical composition of claim 1 wherein the water-soluble polymer further comprises a second hydrophobic group in addition to tocoferol.

10. (Twice Amended) The fluid pharmaceutical composition of claim 1 wherein the [surfactant] tocoferol covalently linked to a water-soluble polymer is d-α-tocopheryl polyethylene glycol 1000 succinate or a derivative thereof.

11. (Amended) The fluid pharmaceutical composition of claim 10 wherein the d-α-tocopheryl polyethylene glycol 1000 succinate is present at a concentration from about 0.02 wt % to about 20 wt %.

12. (Amended) The fluid pharmaceutical composition of claim 10 wherein the d-α-tocopheryl polyethylene glycol 1000 succinate is present at a concentration from about 0.02 wt % to about 10 wt %.

13. (Amended) The fluid pharmaceutical composition of claim 10 wherein the d-α-tocopheryl polyethylene glycol 1000 succinate is present at a concentration from about 4 wt % to about 10 wt %.

14. (Amended) The fluid pharmaceutical composition of claim 1 further comprising a targeting molecule.

15. (Amended) The fluid pharmaceutical composition of claim 14 wherein the targeting molecule comprises a targeting moiety and a lipophilic moiety.

16. (Amended) The fluid pharmaceutical composition of claim 15 wherein the targeting moiety is an antibody, hormone, carbohydrate, drug, cytokine, or interleukin.

17. (Amended) The fluid pharmaceutical composition of claim 15 wherein the targeting moiety is a peptide.

18. (Twice Amended) A method of treating an animal comprising administering to the animal a fluid pharmaceutical composition comprising an aqueous dispersion of micelles having an average diameter less than about 300 nm, said micelles comprising:

> a podophyllotoxin selected from the group consisting of etoposide and teniposide, and [a surfactant selected from the group consisting of tocoferol and] tocoferol covalently linked to a water-soluble polymer; with the proviso that free tocoferol is not present.

19. (Twice Amended) The method of claim 18 wherein the [surfactant is TPGS] tocoferol covalently linked to a water-soluble polymer is d-α-tocopheryl polyethylene glycol 1000 succinate or a derivative thereof.

20. (Twice Amended) A method of delivering a podophyllotoxin selected from the group consisting of etoposide and teniposide to a cell comprising administering to the cell a fluid

pharmaceutical composition comprising an aqueous dispersion of micelles having an average diameter less than about 300 nm, said micelles comprising:

a podophyllotoxin selected from the group consisting of etoposide and teniposide; and [a surfactant selected from the group consisting of tocoferol and] tocoferol covalently linked to a water-soluble polymer; with the proviso that free tocoferol is not present.

21. (Twice Amended) A method of inhibiting cancer comprising administering to an animal having cancer a fluid pharmaceutical composition comprising an aqueous dispersion of micelles having an average diameter less than about 300 nm, said micelles comprising:

a podophyllotoxin selected from the group consisting of etoposide and teniposide; and [a surfactant selected from the group consisting of tocoferol and] tocoferol covalently linked to a water-soluble polymer; with the proviso that free tocoferol is not present.

22. The fluid pharmaceutical composition of claim 1 wherein the micelles have an average diameter less than about 100 nm.

23. The fluid pharmaceutical composition of claim 1 wherein the micelles have an average diameter less than about 50 nm.

24. The fluid pharmaceutical composition of claim 1 wherein the micelles have an average diameter from about 3 nm to about 25 nm.

* * *

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

In re Application of LUTZ, *et al.*

Filed: January 20, 2000

Examiner: J. Kim

Serial No. 09/488,298

Group Art Unit: 1614

For: NOVEL PODOPHYLLOTOXIN COMPOSITIONS

DECLARATION OF DR. VALERY ALAKHOV UNDER RULE 1.132

I, Valery Alakhov, hereby declare that:

1. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, of both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

2. I am Vice-President R&D and Chief Scientific Officer at Supratek Pharma Inc., Montreal, Quebec, Canada H9S 5T8. A full and accurate account of my qualifications including education, publications, titles, and awards, for example, is presented in my curriculum vitae (C.V.) as Appendix A attached hereto.

3. I have intensively studied Drug Delivery and the Medicinal Chemistry of Formulation Development, I have authored, for example, professional peer-reviewed publications including but not limited to, for example, as cited in Appendix A attached hereto.

4. By training and experience, accordingly, I am very familiar with the current state of the art and the ongoing development toward effective formulations and delivery of anti-cancer drugs, including epipodophilotoxins and taxanes.

5. I am familiar with the statements in the present file of United States Application Serial No. 09/488,298, the specification, the claims, as well as the Amendment being filed with this Declaration.

6. I am an inventor on the above-identified pending application.

7. I confirm and attest to the fact, in view of the evidence presented herein, that I have employed d-α-tocopheryl polyetherylene glycol 1000 succinate (TPGS) to solubilize podophyllotoxins and to thereby form a stable dispersion having valuable and unexpected physical and therapeutic properties.

8. I further confirm and attest to the fact, in view of the evidence presented herein, that the addition of alpha-tocopherol (*free* tocopherol) to formulations comprising Etoposide and TPGS dramatically reduces the solubility of Etoposide and lead to phase separation.

9. Generally our aqueous pharmaceutical compositions are formed which comprise Etoposide and/or Teniposide as well as tocopherol covalently linked to a water-soluble polymer (e.g., d-α-tocopheryl polyethylene glycol 1000 succinate), wherein free tocopherol is not present. With regard to our specification as filed, Examples 1-3 of our patent application (pages 33-35) show example formulations of Etoposide and TPGS. No precipitation of the drug occurs in Example 1 (2 mg/ml of Etoposide and 40 mg/ml *i.e.* 4% of TPGS) (Formulation A) when the formulation stored at room temperature for at least 36 hours. Our results further demonstrate in Example 2 (as shown in Table 1, *infra*) that Etoposide is increasingly soluble in solutions of increasing concentrations of TPGS. Our

results demonstrate in Example 3 that Etoposide is stable for longer periods of time in solutions of increasing concentration of TPGS.

Table 1. Etoposide solubility in TPGS solutions.

TPGS %	1%	2%	3%	4%	5%	6%	7%	8%	9%	10%
Etoposide solubility (mg/ml)	1.3 ± 0.15	1.6 ± 0.2	1.75 ± 0.3	2.0 ± 0.15	2.1 ± 0.6	3.0 ± 0.9	4.7 ± 0.35	6.0 ± 0.4	7.7 ± 0.4	8.7 ± 0.9

10. Our results further demonstrate with regard to our specification as filed that an aqueous pharmaceutical composition comprised of Etoposide and TPGS, wherein free tocopherol is not present, exhibits valuable anticancer properties and activity. Example 13 (page 38 of the application) demonstrates results wherein C57BL/6 mice (female six/seven-week-old) were intravenously administered either the clinical form of Etoposide (VEPESID®, Bristol-Myers Squibb; each ml containing 20 mg etoposide; 20 mg polysorbate 80; 650 mg polyethylene glycol 300; 30 mg benzyl alcohol; 2 mg citric acid and 1 ml absolute alcohol *qs*) -or- with one of our example Etoposide Formulations (2 mg/ml of Etoposide and 40 mg/ml *i.e.* 4% of TPGS). The results show unambiguously that the formulation of Etoposide and TPGS, wherein free tocopherol is not present, shows greater efficacy against lung metastasis as compared to VEPESID®.

Table 2. Comparison of the Effects of Etoposide Formulation A and VEPESID® on Lung Metastasis.

Treatment	Treatment Schedule (on day after cell inoculation)	Injection Volume (ml/kg)	Number of Animals	Lung Metastasis Numbers (sample number) on day 13

Control (PBS)	1, 3, 5, 7	10	26	> 50 (5)
Formulation A Carrier	1, 3, 5, 7	10	26	> 50 (5)
Vepesid (15 mg/kg)	1, 3, 5, 7	10	22	> 50 (5)
Formulation A (15 mg/kg)	1, 3, 5, 7	7.5	22*	9.8 ± 4.0 (6)**

11. I further confirm and attest to the fact that Examples 14 and 15 (pages 40-42) of the written description further demonstrate unambiguously that the formulation of Etoposide and TPGS, wherein free tocopherol is not present, is more effective against lung carcinoma that VEPESID; *and*, more effective in reducing the number of metastases than the clinical VEPESID® formulation.

12. Our results further demonstrate in Example 16 (page 42 of the application) that an aqueous pharmaceutical composition comprised of Etoposide, and TPGS, wherein free tocopherol is not present, has improved pharmacokinetics when compared to the clinical VEPESID® formulation. The results particularly demonstrate that more Etoposide is present in plasma of mice that receive an aqueous pharmaceutical composition comprised of Etoposide, and TPGS than those who receive VEPESID.

13. In view of this evidence I therefore confirm and attest to the fact that an aqueous pharmaceutical composition formed comprising Etoposide and/or teniposide, and tocopherol covalently linked to a water-soluble polymer (e.g., d-α-tocopheryl polyethylene glycol 1000 succinate), wherein free tocopherol is not present, is reasonably expected to be, and can successfully be employed in a method of administration to a patient to inhibit cancer.

14. I am familiar with the formulations and preparation methods described by Lambert, *et al.*, in U.S. Patent No.6,458,373.

15. Formulations contemplated by Lambert, *et al.*, in U.S. Patent No.6,458,373 all require *free* tocopherol, and are developed and intended for the administration of Paclitaxel.

16. In view of the evidence presented herein (summarized in Table 3) I confirm and attest to the fact that the addition of alpha-tocopherol (*free* tocopherol) to formulations comprising Etoposide and TPGS dramatically reduces the solubility of Etoposide and lead to phase separation.

Table 3: Etoposide concentration in various formulations

Etoposide formulation	Formulation K (TPGS/ α-tocopherol) According to *Lambert*	Formulation L (α-Tocopherol) According to *Lambert*	Formulation M (Polymers/ α-tocopherol) According to *Lambert*	Formulation N (TPGS) According to *The Instant Invention*
Etoposide concentration [mg/mL]	0.881 ± 0.006	0.243 ± 0.021	0.354 ± 0.005	1.862 ± 0.045

17. Preparation of an Example Lambert, *et al.*, U.S. Patent No.6,458,373 Formulation (Formulation K)

To 10 mg of Etoposide dissolved in 1mL of methanol were added 200mg TPGS dissolved in 1mL of methanol. About 350 mg of α–tocopherol (Sigma, USA) were added to the Etoposide – TPGS mixture. Then methanol was evaporated to dryness using a speed-vac concentrator. To the residue was added 5 mL of phosphate buffer saline (PBS) and the mixture was shaken gently for complete dispersion at room temperature for 30 min. The final formulation became milky within one minute after dissolution and started to precipitate in 1.5 hours. The sample was centrifuged at 14,000 rpm 15 minutes.

An aliquot (100 μL) of supernatant was extracted with 900 μL of methylene chloride for 10 minutes. After centrifugation at 10,000 rpm for 10 min, the organic phase containing Etoposide was separated and evaporated to dryness under a stream of nitrogen at 40^0 C. The dry extracts obtained were dissolved in 1 mL of mobile phase. Finally the samples were analyzed for Etoposide concentration using reverse phase HPLC with fluorescence detection. Separation was achieved using a C_{18} column (Phenominex Luna C18(2); 250 x 4.6 mm) at 40^0C and a mobile phase consisting of 25% buffer A (0.1% acetic acid in acetonitrile) / 75% buffer B (0.1% acetic acid in water) at a flow rate of 1.0 ml/min. The excitation and emission wavelengths were set at 230 and 323 nm, respectively. The amount of Etoposide in each sample was calculated from area under the peak (AUP) using a calibration curve for Etoposide. The results are shown in Table 3, *supra*.

18. Preparation of an Example Lambert, *et al.*, U.S. Patent No.6,458,373 Formulation (Formulation L)

To 10 mg of Etoposide dissolved in 1mL of methanol were added 350 mg of α–tocopherol (Sigma, USA). Then methanol was evaporated to dryness using a speed-vac concentrator. To the residue was added 5 mL of phosphate buffer saline (PBS) pH 5.5 and the mixture was shaken gently for complete dispersion at room temperature for 30 min. Immediately after dissolution, the final formulation separated into two phases and was insoluble for the entire period of time. The sample was centrifuged at 14,000 RPM for 15 minutes.

Extraction and HPLC analysis of sample was the same as in 17. The results are shown in Table 3, *supra*.

19. Preparation of an Example Lambert, *et al.*, U.S. Patent No.6,458,373 Formulation (Formulation M)

In 150 µl of methanol was dissolved 2 mg of Etoposide and then 200 µl of 10% solution of Pluronic P104 in methanol and 100 µl of 10% solution of Pluronic F87 in methanol were added to the Etoposide solution. About 70 mg of α–tocopherol (Sigma, USA) were added to the Etoposide – polymer mixture. The mixture was evaporated to dryness using a speed-vac concentrator. To the residue was added 1 ml of PBS and the mixture was dissolved using a rotator. The formulation showed formation of white chunky precipitate on the walls and bottom of vial within 10 minutes after dissolution.

The sample was centrifuged at 14,000 RPM for 15 minutes. Extraction and HPLC analysis of sample was the same as in 17. The results are shown in Table 3, *supra*.

20. Preparation of an Example Formulation of the Present Invention (within the scope of the claims presented herewith) (Formulation N)

To 10 mg of Etoposide dissolved in 1mL of methanol were added 200mg TPGS dissolved in 1mL of methanol. Then methanol was evaporated to dryness using a speed-vac concentrator. To the residue was added 5 mL of phosphate buffer saline (PBS) and the mixture was shaken gently for complete dispersion at room temperature for 30 min. The final formulation was a clear and transparent liquid slightly yellowish colored. The formulation did not show any precipitation of drug when stored at room temperature for at least 36 hours.

The sample was centrifuged at 14,000 RPM for 15 minutes. Extraction and HPLC analysis of sample was the same as in 17. The results are shown in Table 3, *supra*.

21. I further present evidence and confirm and attest to the fact that that formulations of the present invention, within the scope of the claims presented herewith, while being appropriate for Etoposide, do not provide sufficient solubility to Paclitaxel, which is contrary to compositions described and contemplated by Lambert, *et al.*, in U.S. Patent No.6,458,373.

22. Preparation of Paclitaxel formulation (Formulation O)

To 10 mg of Paclitaxel dissolved in 1mL of methanol were added 200mg TPGS dissolved in 1mL of methanol. About 350 mg of α–tocopherol (Sigma, USA) were added to the Paclitaxel –TPGS mixture. Then methanol was evaporated to dryness using a speed-vac concentrator. To the residue was added 5 mL of phosphate buffer saline (PBS) pH 5.5 and the mixture was shaken gently for complete dispersion at room temperature for 30 min. The final formulation became milky within one minute after dissolution and started to precipitate in 1.5 hours.

23. Preparation of Paclitaxel formulation (Formulation P)

To 10 mg of Paclitaxel dissolved in 1mL of methanol were added 200mg TPGS dissolved in 1mL of methanol. Then methanol was evaporated to dryness using a speed-vac concentrator. To the residue was added 5 mL of phosphate buffer saline (PBS) and the mixture was shaken gently at room temperature for 30 min. The final formulation became milky within one minute after dissolution and started to precipitate in 1 hour.

Respectfully submitted,

By: _____

Date: 28.05.07

DR. VALERY ALAKHOV

APPENDIX A

CURRICULUM VITAE

VALERY Yu. ALAKHOV, Ph.D.

Present Position : Vice-president and CSO,
Supratek Pharma Inc.
Montreal, Quebec, Canada

Personal Data

Date and place of birth : October 7, 1957
Uzghorod, Ukraine

Citizenship : Canadian

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Tel: (450) 686 5502, Fax: (450) 686 5504
e.mail: **Valery.Alakhov@Supratek.com**

Education History

1986	:	Ph.D., Molecular Biology, Institute of Molecular Biology, USSR Academy of Sciences, Moscow, Russia
Title	:	Factors of Regulation of Calmodulin-Dependent Enzymes,
Research adviser	:	Prof. E.S.Severin, Ph.D., Dr.Sc.
1982	:	M.Sc., Organic Chemistry Moscow Institute of Fine Chemical Technology Moscow, Russia
Title	:	Complete Amino Acid Sequence of Calmodulin from Human Brain
Research adviser	:	Prof. E.S.Severin, Ph.D., Dr.Sc.

P stdoct ral Research Training

1990	:	Post-Doctoral Fellow, Biochemistry Department, German Cancer Research Center, Heidelberg, Germany, Biochemistry
1991 - 1992	:	Invited Scientist, Laboratory of Cancerology, Biochemistry Department, Laval University, Quebec, Quebec, Canada Cell Biology

Research and Academic Positions

1994-pres.	:	Director, Vice-president R&D and Chief Scientist Supratek Pharma Inc. Montreal, Quebec, Canada
1994-pres.	:	Associate professor, Immunology Research Center Institute Armand-Frappier University of Quebec Laval, Quebec, Canada
1986 - 1993	:	Senior Scientist (1986-1988), Head, Laboratory of Protein Interactions (1988-1992) Director, Department of Drug Targeting (1992-1993) Russian Research Center of Molecular Diagnostics and Therapy Moscow, Russia
1982 - 1986	:	Junior Research Fellow, Laboratory of Enzyme Regulation of Cell Activity, Institute of Molecular Biology, USSR Academy of Sciences, Moscow, Russia

P stdoctoral Experience : 16 years

Teaching Experience :Scientific supervision of 12 Ph.D students and 5 M.Sc. students

Research Grants (in Canada)

1999	:	IRAP NRC
1996	:	IRAP NRC
1996	:	IRAP NRC
1994	:	IRAP NRC
1993	:	FRSQ
1991	:	MRC

Professional Organisations

1982-pres.	:	Russian Biochemical Society
1986-pres.	:	Russian Immunological Society
1992-pres.	:	American Cancer Society
1995-pres	:	Canadian Society for Immunology
1996-pres.	:	American Society of Pharmaceutical Sciences
	:	American Association for the Advancement of Science
1998-pres.	:	American Chemical Society

Areas of expertise and scientific interests

Fundamental research in the areas of drug resistance; cancer progression and genetic instability.

Applied research at the interface of formulation and material sciences, polymer chemistry, colloidal chemistry, molecular, cell-free and cellular biology.

Development of physical, chemical and biological assay systems including formulation assays (drug chemical and physical stability); ADME assays (drug serum protein interaction; drug metabolic conversion; pharmacokinetics and pharmacodynamics; toxicopharmacology, etc); biological cell-free assays (in vitro transcription/translation, phage display, gene expression profiling); biological cell-based assays (intestinal and cerebral drug transport; apoptosis;

angiogenesis; cytotoxicity; etc.); in vivo assays (ADME analysis; tumor and inflammation models).

Industrial and management experience

Planning and supervision of R&D work both for in-house and collaborative (big pharma and biotech companies) projects.

Managing R&D budget of up to $5M/year.

Supervising a small-to-medium (up to 40 scientists) multidisciplinary R&D group.

Supervision of the in-house work under GLP principles.

Supervision of outsourced projects under GMP compliances.

Preparation of US and Canadian IND and European CTX submissions.

Managing (on the sponsor side) the work of CRO and clinical investigators in clinical trial Phase I and Phase II setting in oncology.

Publications

More than 70 scientific publications in peer reviewed international journals; 11 issued US patents, many US and international patents are pending.

References:

Available upon request.

Selected Articles and Reviews

Reviews

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